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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/494,332	01/28/2000	Kevin M. Gorman		3281

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EXAMINER
GOLDBERG, JEANINE ANNE

ART UNIT	PAPER NUMBER
1634	29

DATE MAILED: 09/13/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/494,332	Applicant(s) GORMAN ET AL.	
	Examiner Jeanine A Goldberg	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/1/02; 2/19/02* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *25 and 46* is/are allowed.

6)☒ Claim(s) *1-24,26-31,33,35,37,39,41 and 43-45* is/are rejected.

7)☒ Claim(s) *32,34,36,38,40 and 42* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed February 19, 2002; July 1, 2002. Currently, claims 1-46 are pending. All arguments and the declaration by Kevin M. Gorman, filed February 19, 2002 have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 19, 2002 has been entered.

3. It is noted that no new arguments or amendments have been filed subsequent to the advisory action. Therefore, this action is **FINAL.**

Maintained Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1-15 and 43-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Han et al (PNAS, Vol. 88, pg. 1711-1715, March 1991) or Maertens

et al (US Pat. 5,846,704, December 1998) and Backus et al (US Pat 6,001,558, December 1999) in view of Nedjar et al (J. of Virological Methods, Vol. 35, No. 3, pg 297-304).

Han et al. (herein referred to as Han) teaches the sequence of 341 base pairs from the 5' untranslated region (UTR) of HCV and alignment of this sequence from several different HCV isolates. Han teaches extracting the plasma from HCV-positive or negative blood donors. RNA was isolated and converted into single-stranded cDNA by reverse trancriptase using the appropriate cDNA primer (pg 1711, col 2). Han teaches primers for the PCR amplification of 5' UTR and means of cloning these PCR products (pg. 1711, col. 2, and Figure 2). The PCR products were analyzed by southern blot hybridization using a labeled oligonucleotide probe (pg 1711, col 2). Han teaches that when the sequence of the 5' UTR is compared among isolates, there is a high degree of sequence homology and that the sequence mismatches that are present are clustered in 5 positions, as taught in Figure 2 (see also pg. 1713, para 1). Han teaches that the 342 base pair 5' UTR sequence represents a signature sequence that could serve as a HCV-specific DNA probe for the detection of all strains of the virus and further that the primers and highly reliable PCR protocol method as taught could be used for this purpose (pg 1714, para 4).

Maertens et al (US Pat. 5,846,704, December 8, 1998) teaches a method of genotyping of HCV isolates using probes targeting sequences from the 5' UTR region of HCV (abstract). Maertens teaches extracting viral DNA from serum such that RNA was pelleted (col 24, lines 60-68). Random primers were then added such that cDNA was

synthesized (col 24, lines 60-68). Maertens teaches amplifying the cDNA with outer primers and subsequently inner primers (col. 25, lines 5-10). The PCR product was then subjected to electrophoresis in an agarose gel and ethidium bromide staining (col. 25, lines 14-15). Furthermore, strips of immobilized HCV-specific primers developed and hybridized with PCR amplified DNA fragments of the 5' UTR for visualization (col. 25, lines 50-60). Maertens teaches a kit which comprises a set of primers, a set of probes immobilized on a solid substrate, and buffers (col. 20, lines 45-55). Maertens provides specific primers for each of the isolates and universal primers which may be used (Table 4 and 5). SEQ ID NO: 1 of the instant application overlaps SEQ ID NO: 27 of Maertens. Nucleotides 17-25 of the instant application are identical to nucleotides 1-9 of Maertens. SEQ ID NO: 2 of the instant application overlaps SEQ ID NO: 4 of Maertens. Nucleotides 5-25 of the instant application are identical to nucleotides 1-20 of Maertens.

Backus et al. (herein referred to as Backus) teaches amplification and detection of HIV-1 and HIV-2. Backus teaches oligonucleotides, namely SEQ ID NO: 2 and 4, which amplify HIV-1 nucleic acids including oligonucleotides which are instant SEQ ID NO: 3 and 5. Backus also teaches an oligonucleotide, namely SEQ ID NO: 3, which comprises the nucleotides of instant SEQ ID NO: 4. Backus, furthermore, teaches oligonucleotides which amplify HIV-2 nucleic acids including oligonucleotides, namely SEQ ID NO: 14 and 16, which are instant SEQ ID NO: 6 and 7. Backus also teaches oligonucleotide probes, namely SEQ ID NO: 5, 17, 6, which are instant SEQ ID NO: 13, 14 and 16 for HIV-1 and HIV-2. The primers chosen were from identified highly

conserved sequence regions (col. 10, lines 50-60). Backus teaches that a biological sample is used which included cellular-or viral material, hair, body fluids, or cellular material containing nucleic acids which may be detected (limitations of Claims 8 and 23).

Han and Backus do not specifically teach co-amplifying or co-detecting HCV and HIV using the primers of the instant claimed invention.

However Nedjar teaches a method of co-amplification of specific sequences of HCV and HIV by using PCR assays. Nedjar teaches that primer pairs from HCV and HIV-1 sequences were used (pg 299). Nedjar teaches the conditions of the multiplex reaction. Nedjar teaches the ability to co-amplify specific sequence from two different viral genomes in the same reaction mixture offers the possibility of simultaneous detection and diagnosis of more than one viral agent in serum samples of infected individuals.

Further, in the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the court determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologues, however, the court stated

> "Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologues because homologues often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed oligonucleotides simply represent functional equivalents of primers 89 and 51 of Han or SEQ ID NO: 4 and 27 of Maertens for amplifying the 5' UTR region of HCV and of SEQ ID NO: 2-4, 14-16 of Backus for amplifying HIV-1 and HIV-2, in which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited reference. Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Han or Maertens and Backus in view of Nedjar to obtain the claimed invention as a whole. The skilled artisan would have been motivated to have used primers from the 5' UTR region to detect HCV, as taught by Han and Maertens and primers from HIV-1 and HIV-2 as taught by Backus. Since Han provides an alignment of several isolates which show conserved regions between the isolates, and delineates the ORFs, the ordinary artisan would have been motivated to have designed primers which amplify various regions of interest from the 5' UTR region. Specifically, the skilled artisan would have chosen instant SEQ ID NO: 1 and 2, which flank ORF3. Moreover, the primer SEQ ID NO : 4 of Maertens encompass 20/25 of instant SEQ ID NO: 2 and primer SEQ ID NO: 27 encompasses 6/25 nucleotides of instant SEQ ID NO: 1. Furthermore, the skilled artisan would have chosen SEQ ID NO: 11, 12 or 13 for probing the detection of HCV. The ordinary artisan would have been motivated to amplify the 5' UTR region of HCV since Han teaches that the 342 base pair 5' UTR sequence represents a signature sequence that could serve as a HCV-specific DNA probe for the detection of all strains of the virus and further that the primers and highly

reliable PCR protocol method as taught could be used for this purpose. The ordinary artisan would have used the probes and primers from Backus which either comprises or encompass the instant SEQ ID NO:s 3-7, 13-14, 16, based upon the detailed analysis provided that these probes and primers were for conserved regions among the numerous isolates. The ordinary artisan would have combined the teachings of Han or Maertens and Backus in view of Nedjar for the express benefit of diagnosing more than one viral agent in samples of infected individuals. The ordinary artisan would have recognized that the detection of more than one viral agent would have been ideal for saving time, and reagents. The multiplexing of numerous primers into a single reaction has the express benefit of saving reagent by limiting the number of assays and also saving time of scientists since the results may be obtained simultaneously. Thus, the ordinary artisan would have combined the teachings of detecting HCV with the teachings of detecting HIV-1 and HIV-2.

Response to Arguments

The response traverses the rejection and provides a declaration under 1.132 by Kevin Gorman, filed February 19, 2002. The examiner has fully considered to request for reconsideration and the declaration by Gorman. The arguments and the declaration are not found persuasive. When all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness. As provided by MPEP 716.02(e), "An affidavit or declaration under 37 CFR 1.132 must compare the claimed subject matter with the closest prior art to be effective to rebut a prima facie case of obviousness. In re Burckel, 592 F.2d 1175, 201 USPQ 67 (CCPA

1979)." The instant declaration, while providing a comparison, compares a multiplex reaction with primers of SEQ ID NO: 1-5, wherein primers 1-2 are directed to the 5'NC region of HCV with a multiplex reaction with primers 3-5 and primers directed to the 3'NC region of HCV. The comparison is between two separate regions of the HCV genome: the 5' non-coding region and the 3' non-coding region (page 4 of declaration filed February 19, 2002). The obviousness rejection of record is directed to picking primers within the 5'NC region of HCV and within HIV-1 or HIV-2. Thus, illustration that a multiplex reaction with primers in the 3'NC region of HCV is not the closest prior art to multiplex analysis with HIV. A comparison between the primers within the 5'NC of HCV taught in the art and the HIV-1 or HIV-2 primers taught in the art would be the closest prior art. In essence a comparision has not been done with the prior art directed to the 5'NC region of HCV, but rather to distinct prior art directed to the 3'NC region of HCV. Furthermore, it is noted that the claims are do not require co-amplification of the nucleic acids.

Additionally, the declaration directed to specific SEQ ID NO: 1-5 are not commensurate in scope with the claims. As provided by MPEP 716.02 (d), "Whether the unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, the "objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support." In other words, the showing of unexpected results must be reviewed to see if the results occur over the entire claimed range." The claims are broadly drawn to probes and primers comprising SEQ ID NO: 1-7, for example. The primers consisting of SEQ ID

NO: 1-5 is not commensurate in scope with primers comprising SEQ ID NO: 1-5. Similarly, it is noted that the claims are not limited to co-amplification of the nucleic acids.

Han and Maertens teaches the full length 5'UTR region of HCV with specific probes and primers within the nucleic acid. Backus teaches probes and primer which either consist of the instant SEQ ID NO:s 3, 5-7, 13-14, and16 or comprise SEQ ID NO: 4. The prior art provides specific guidance regarding the use of primers and probes from this region of the HCV genome for detection purposes. With respect to the HIV-1 and HIV-2 probes and primers, Backus teaches SEQ ID NO: 3, 5-7, 13-14, 16 of the instant application and a nucleic acid comprising SEQ ID NO: 4 of the instant application. The art has provided specific motivation and teachings to choose the probes and primers for the HIV-1 and HIV-2 detection. Therefore, for the reasons above and those already of record, the rejection is maintained.

5. Claims 31, 33, 35, 37, 39, 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Han et al (PNAS, Vol. 88, pg. 1711-1715, March 1991) or Maertens et al (US Pat. 5,846,704, December 1998) and/or Backus et al (US Pat 6,001,558, December 1999) in view of Nedjar et al (J. of Virological Methods, Vol 35, No. 3, pg 297-304) as applied to Claim 1-15, 43-44 above, and further in view of Ahern (www.thescientist.library.upenn.edu/yr1995/july/tools_950724.htlm, December 22, 1998).

Neither Han, Maertens, Backus nor Nedjar specifically teaches packaging necessary reagents into a kit.

However, Ahern teaches reagent kits offer scientists good return on investment. Ahern teaches kits save time and money because the kits already comes prepared.

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the teachings of Han, Maertens and Backus in view of Nedjar with the teachings of Ahern to incorporate the necessary reagents into a packaged kit. The ordinary artisan would have been motivated to have packaged the primers, probes, and reagents of Han, Maertens and Backus into a kit, as taught by Ahern for the express purpose of saving time and money.

Response to Arguments

The response traverses the rejection. The response asserts that Ahern does not overcome any of Han's, Maertens', Backus', or Nedjar's deficiencies. Specifically the response asserts that Ahern does not teach or suggest any prepackaged PCR kit and specifically not a kit containing the particular probes and primers of the instant invention. This argument has been reviewed but is not convincing because the teachings of Ahern specifically teach packaging reagents necessary for a reaction into a kit. Thus, the ordinary artisan would have packaged the necessary reagents, primers, taught by Han or Maertens and/or Backus in view of Nedjar into a kit for all of the reasons of Ahern. Thus for the reasons above and those already of record, the rejection is maintained.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 1-15 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-64 of copending Application No. 09/493,353. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications are directed to a method of detecting HCV 5' UTR using SEQ ID NO: 1 and 2 of the instant application which are identical to SEQ ID NO: 2 and 7 of 09/493,353.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

The response traverses the rejection. The response asserts that upon allowable subject matter in the two cases, Applicant's agree to submit a terminal disclaimer. Thus for the reasons above and those already of record, the rejection is maintained.

Allowable Subject Matter

7. The instant IPC region and primers to the synthetic region are novel over the prior art. The SEQ ID NO: 8, 9 and 15 are not previously known in the art. However, Picone et al. (US Pat. 5,491,225, February 1996) and Blasczyk et al (Beitrage Zur Infusionstherapie Und Transfusionmedizin, Vol 34, pg 236-241, 1997-abstract only) teach incorporating IPC RNA into an assay. Picone et al. (herein referred to as Picone) teaches "internal positive control oligonucleotide sequences" are a recombinant or synthetic oligonucleotides that ensure assay users that the amplification process has occurred in the event that the sample being tested has no target nucleic acid. Additionally, Blasczyk et al. (herein referred to as Blascyzk) teaches a pair of primers which amplify a fragment of the human growth hormone gene was included as an internal positive amplification control. The presence or absence of specific PCR amplification allowed definite allele assignment without the need for any post-amplification specificity step. Additionally, Blasczyk teaches that the internal positive control primers indicate a successful PCR amplification (abstract). Thus, while the concept of internal control regions and primers to amplify are known in the art, the specific sequences of the instant used primers are novel.

Conclusion

8. **Claims 16-31, 45-46 are allowable over the prior art.** Claims **32, 34, 36, 38, 40, 42, are** objected to as being dependent upon a rejected base claim, but would be

allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

9. Claims 1-15, 33, 35, 37, 39, 41, 43-45 are not allowable.

10. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Enewold Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Thursday from 7:00AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J. Goldberg

Jeanine Enewold Goldberg
September 4, 2002

W. Gary Jones
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